REMARKS

Claims 1-5, 8-19 and 38 were pending in this application. After entry of the amendments herein, claims 1, 8-15, 38 and 41 will be pending in this application. Claims 2-5 and 16-19 have been canceled. Claims 1, 8-13 and 15 have been amended and new claim 41 has been added. Support for the amendments and new claim 41 can be found throughout the specification. No new matter has been added.

Claims 1-4, 8, 10, 12, 13, 18 and 38 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fung *et al.*, (US 4,757,141). As claims 2-5 and 16-19 have been canceled, rejection of claims 2-4 and 18 has been rendered moot. Claims 1 and 13 have been amended to include a S-acetyl-2-thioethyl (SATE) protected phosphate thereby rendering the rejection of claims 1, 8, 10, 12, 13 and 38 moot.

Claims 1, 13, 18 and 38 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Groody (EP 0 266 168). As claim 18 has been canceled, rejection of this claim has been rendered moot. Claims 1 and 13 have been amended to include a SATE protected phosphate thereby rendering the rejection of claims 1, 13 and 38 moot.

Claims 1-5, 13, 18 and 19 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iyer *et al.*, (WO 96/07392) in view of Tosquellas *et al.*, (Nucleic Acids Research 1998, Vol. 26, pages 2069-2074). As claims 2-5 and 16-19 have been canceled, rejection of claims 2-5, 18 and 19 has been rendered moot. Applicants respectfully traverse this rejection because one of ordinary skill in the art would not have been motivated to combine the Iyer *et al.*, published international application and the Tosquellas *et al.*, article in the manner suggested in the Office action to produce a single stranded oligomeric compound or a double stranded composition having a SATE protected phosphate at a 5'-terminus.

The Iyer *et al.*, published international application is directed to preparing oligonucleotide prodrugs having one or more lipophilic groups attached to an internucleotide phosphate (or other) linkage. The application further discloses that the lipophilic group can be attached to a 3' or 5'-phosphate group. Iyer states in the application at page 13, starting at line 20, that "The present invention provides a method of improving oligonucleotide uptake through lipid membranes into cells..." and teaches that by adding lipophilic groups (at least one) to oligonucleotides their cellular uptake is improved.

The Tosquellas *et al.*, application is directed to selected 12mer oligonucleotides having a SATE group at each internucleoside linkage. These oligonucleotides had increased stability in calf spleen and snake venom phosphodiesterases and were selectively hydrolized to the anionic parent oligonucleotides upon treatment with CEM cell extracts.

The Office action has characterized Iyer as teaching oligonucleotide prodrugs that have increased cellular uptake and react with cellular enzymes to generate a natural phosphodiester. The data provided describes the enzymatic stability of a small group of oligonucleotides having small lipophilic groups attached thereto that have been treated with for example serum, porcine liver esterase or snake venom phosphodiesterase. There is no data supporting that these small groups would actually enhance uptake into cells. Covalently bound lipophilic conjugates are generally very large molecules such as steroids, long chain lipids and such. The ability of certain lipid conjugates to increase cellular uptake is well established in the art (prior to the Iyer *et al.*, application) for example see Antisense Research and Applications, Stanley T. Crooke and Bernard Lebleu eds., CRC Press, Ann Arbor, Copywright 1993, page 166, b. Lipophilic Groups at the 3' and/or 5' terminals of the oligonucleotide.

Hence, the invention actually taught by Iyer *et al.*, is a linkage that attaches a lipid group to an oligonucleotide that provides serum stability and intracellular lability. Each example of the linkages taught by Iyer *et al.*, comprise the formula R-C(=O)-CH_2-X-P, where X is O or S and P is the phosphorus group of the internucleotide linkage. In each of the figures X is attached to a single methylene followed by an acyl (R-C(=O)-) group or an unsaturated ring system (see figures). The linkage taught by Iyer et al., does not comprise two consecutive methylene groups attached to a heteroatom (X) attached to phosphorus as required by the present invention.

It would not have been obvious to substitute lipophilic groups at the 5'-position as taught by Iyer *et al.*, with a SATE protecting group as taught by Tosquellas *et al.* As discussed above the actual invention of Iyer *et al.*, is an intracellularly cleavable linkage that is useful for attaching different lipophilic groups. The substitution of the SATE group for the lipophilic linked groups of Iyer *et al.*, would render lipid substitution impossible as the SATE groups are not taught as variable linker groups having different lipid groups attached thereto. Those skilled in the art would realize that such substitution would negate the invention of Iyer *et al.* In the Tosquellas *et al.*, article with each (x11) internucleoside linkage is modified to have a SATE group attached thereto. The Tosquellas *et al.*, article concludes that one can

only hypothesize as to the bioavailability of such modified oligonucleotides as compared to an unmodified oligonucleotides and that much more work, including *in vivo* work, needs to be performed before a definitive conclusion can be reached. Hence the Tosquellas *et al.*, article actually teaches away from combination with the Iyer *et al.*, application.

Claims 1-4, 8-13, 18 and 38 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Boutla *et al.*, (Current Biology 2001) in view of Iyer *et al.*, (WO 96/07392). As the amended claims have been limited to SATE phosphorus protecting groups this rejection has been renedered moot.

Claims 1-4, 8-18 and 38 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Boutla *et al.*, (Current Biology 2001) and Iyer *et al.*, (WO 96/07392) as applied to claims 1-4, 8-13, 18 and 38 above, and further in view of Parrrish *et al.*, (Molecular Cell 2000). As the amended claims have been limited to SATE phosphorus protecting groups this rejection has been renedered moot.

Applicants respectfully assert that the claims are now in condition for allowance, and earnestly request early reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-0252.

Respectfully submitted,

Robert S. Andrews

Robert S. Andrews
Registration No. 44,508

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ISIS Pharmaceuticals, Inc.
1896 Rutherford Rd.
Carlsbad, CA 92008
Telephone: (760) 931-9200
Facsimile: (760) 603-3820